Roger Williams MEDICAL CENTER

Roger Williams Hospital

Department of Surgery

825 Chalkstone Avenue
Providence
Rhode Island 02908-4735
(401) 456-2507
(401) 456-5395 FAX

Richard P. Junghans, Ph.D., M.D.
Chief, Division of Surgical Research
Associate Professor of Surgery and Medicine
Director, Biotherapeutics Development Lab

May 4, 2005

Director
United States patent and Trademark Office
Washington DC 20231

Attn: Dr. Larry Helms, Examiner

RE: "Antibodies as chimeric effector cell receptors against tumor antigens" #10/006,773

Dear Dr. Helms:

I am returning materials related to the USPTO action dated 2/18/2005 along with a check for the extension fee. This submission complies with the extension penalty requirement.

Thank you for your time and consideration.

Sincerely,

Richard P. Junghans, PhD, MD

Enclosure

RPJ/mj

05/10/2005 RMEBRAHT 00000009 10006773
01 FC:2252 225.00 OP

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No. 10/006,773	Applicant(s) JUNGHANS, RICHARD P.	
	Examiner Larry R. Helms	Art Unit 1642	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

The amendment document filed on *25 January 2005* is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☒ 1. Amendments to the specification:
  - ☒ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☐ 3. Amendments to the drawings:
  - ☐ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☒ 4. Amendments to the claims:
  - ☐ A. A complete listing of all of the claims is not present.
  - ☐ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☐ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☒ E. Other: *claims 8 and 9 do not have the added material underlined and the material removed lined through or bracketed as required in MPEP 714*.

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714 and the USPTO website at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf .

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance. If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted within the time period set forth in the final Office action.

2. Applicant is given **one month**, or thirty (30) days, whichever is longer, from the mail date of this notice to supply the **corrected section** of the non-compliant amendment in compliance with 37 CFR 1.121, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a *Quayle* action.

Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.

Failure to timely respond to this notice will result in:
Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or
Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

LARRY R. HELMS, PH.D
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,773	12/10/2001	Richard P. Junghans		2051

7590 02/18/2005

Richard P. Junghans, Ph.D., M.D.
One Lyndeboro Place
Boston, MA 02116

EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Date: January 25, 2005

RESPONSE TO DETAILED ACTION

1. Terms will be amended to "method" instead of "use". A clean copy of the claims are appended.
2. We have attached a listing of Figures modified with sequence references attached.

ELECTIONS/ RESTRICTIONS

3. We elect Group II, with traverse. In item #4., we argue that these are not four groups.
4. The four groups as outlined are related by use of a chimeric gene structure in which they are distinguished by sequence of the antibody region. Three bind to one antigen (PSMA) and one binds to another antigen (GD3). We view these as specific analogous agents from this laboratory to be covered as separate sub-claims under a single patent application.
5. For response, see 4.

We submit the following amended Figures to include sequence references.

Fig.3 **(presently amended)** shows diagram and DNA sequence of a chimeric sFv IgTCR, including the CD8α hinge modified-to-remove cysteines, within a retroviral vector. This example IgTCR molecule (using hMN14 antibody specific to CEA antigen, not part of this application) occupies nucleotides ~~2426~~ **2428** to ~~3766~~ **3756**. **(Sequences #1, 2;** the vector sequences are incidental.) Equivalent versions using the antibodies MB3.6, 3D8, 4D4, 3E11 are prepared in analogous manner to create IgTCR, or other Ig-chimeric molecules.

Fig.4 **(presently amended)** shows the DNA sequence of:

A., B. leader plus VH **(seq. #3, 4)** and leader plus VL **(seq. #5, 6)** that specifies MB3.6.

C. As example, the VL and leader are joined with **(GGSGS)3** linker to VH to create MB3.6 sFv as shown **(seq. #7, nucleotides shown for amino acid seq (GGSGS)3),** that is subsequently used in creating chimeric molecules. Other means of generating sFv are possible and included under this claim, as well as other means of creating antibody chimeric molecules under the intent of this invention.

D., E. leader plus VH **(seq. #8, 9)** and leader plus VL **(seq. #10, 11)** that specifies 3D8 (includes C domain sequences).

F., G. leader plus VH **(seq. #12, 13)** and leader plus VL **(seq. #14, 15)** that specifies 4D4 (includes C domain sequences).

H., I. leader plus VH **(seq. #16, 17)** and leader plus VL (seq. #18, 19) that specifies 3E11 (includes C domain sequences).

These sequences are modified to prepare the sFv used in Fig.1 and Fig.3, and similarly for other constructs.

We submit the following amended claims:

Claims

What is claimed is:

1. (previously presented) A chimeric molecule comprised of the GD3 binding domain of antibody MB3.6, with variable gene sequences as specified in Fig.4A-C, as a single chain antibody with a (GGSGS)3 linker, the zeta signaling chain of the T cell receptor and an intervening CD8α hinge in which the cysteine residues have been mutated.

2. (previously presented) A chimeric molecule comprised of the PSMA binding domain of antibody 3D8, with variable gene sequences as specified in Fig.4D&E, as a single hchain antibody with a (GGSGS)3 linker, the zeta signaling chain of the T cell receptor and an intervening CD8α hinge in which the cysteine residues have been mutated.

3. (previously presented) A chimeric molecule comprised of the PSMA binding domain of antibody 4D4, with variable gene sequences as specified in Fig.4F&G, as a single chain antibody with a (GGSGS)3 linker, the zeta signaling chain of the T cell receptor and an intervening CD8α hinge in which the cysteine residues have been mutated.

4. (previously presented) A chimeric molecule comprised of the PSMA binding domain of antibody 3E11, with variable gene sequences as specified in Fig.4H&I, as a single chain antibody with a (GGSGS)3 linker, the zeta signaling chain of the T cell receptor and an intervening CD8α hinge in which the cysteine residues have been mutated.

5. (previously presented) Molecules of claim 1-4 in which other signaling chains of T cells or other cell types are substituted, or in which a different hinge molecule or no hinge molecule is substituted, or a combination thereof.

6. (previously presented) Molecules of claim 1-5 in which at least one of the CDRs of the heavy chain and one of the CDRs of the light chain are preserved in a form (e.g., sFv or Fab) that maintains the binding of the antigen, and/or in which the linker is of different composition. For MB3.6, this specification may be met by one CDR of the heavy chain to maintain antigen binding because of the small size of the ganglioside antigen.

7. (previously presented) Molecules of claim 1-6 which has been modified in DNA or protein sequence but which retains the specificity and action of these molecules.

8. **(presently amended)** The ~~use of~~ **methods of applying** molecules of claims 1-7 expressed in T cells or NK cells or other effector cells to treat patients with cancers expressing the GD3 (MB3.6 derivatives) or PSMA antigen (3D8, 4D4, 3E11 derivatives).

9. **(presently amended)**. The ~~combination use of~~ **methods of applying** of molecules of claims 1-7 expressed in T cells or NK cells or other effector cells to treat patients with cancers expressing the GD3 (MB3.6 derivatives) or PSMA antigen (3D8, 4D4, 3E11 derivatives), together with with heterologous constructs to engage additional stimulatory and functional properties of the effector cells to enhance the antitumor therapeutic efficacy.